In the Specification

Applicants present replacement paragraphs below indicating the changes with insertions indicated by underlining and deletions indicated by strikeouts.

Please replace the paragraph on page 25, lines 11-35, with the amended paragraph as follows:

All short tandem repeat (STR) genetic markers are di- or tetranucleotide repeat polymorphisms. Information concerning the genetic markers used in this study was obtained from several sources on the internet: Genome Database (GDB, gdbwww.bdb.org ~~The Genome Database, Johns Hopkins University School of Medicine, 2024 E. Monument Street, Suite 1-200, Baltimore, MD 21205-2100, USA~~), GenBank (ncbi.nlm.nig.gov ~~National Center for Biotechnology Information, National Library of Medicine, Building 38A, Bethesda, MD 20894~~), Cooperative Human Linkage Center (CHLC, www.chlc.org ~~The CHLC Project, National Center for Biotechnology Information, National Library of Medicine, Building 38A, Bethesda, MD 20894~~), Eccles Institute of Human Genetics (EIHG, www.genetics.utah.edu/ ~~University of Utah, 15 North 2030 East, Room 2100, Salt Lake City, UT 84112-5330~~) and Généthon (www.genethon.fr/~~1bis, rue de l'internationale, BP 60, 91002 Evry cedex, France~~). Standard PCR was performed in a 25 μl volume containing 100 ng genomic DNA, 200 mM of each dNTP, 1.25 mM $MgCl_2$, 30 pmol of each primer and 0.2 units Goldstar DNA polymerase (Eurogentec). One primer was end-labelled before PCR with [gamma-^{32}P]ATP and T4 polynucleotide kinase. After an initial denaturation step at 94°C for 2 min, 27 cycles were performed at 94°C for 1 min, at the appropriate annealing temperature for 1.5 min and extension at 72°C for 2 min. Finally, an additional elongation step was performed at 72°C for 5 min. PCR products were detected by electrophoresis on a 6% denaturing polyacrylamide gel and by exposure to an X-ray sensitive film. Successfully analysed STSs, STRs and ESTs covering the refined candidate region are fully described herein on pages 36 to 54.

Please replace the paragraph on page 26, line 24 through page 27, line 12, with the amended paragraph as follows:

Growing of YACs and extraction of YAC DNA was done according to standard protocols (Silverman, 1995). For the construction of the YAC-contig spanning the chromosome 18q candidate region, the data of the physical map based on sequence tagged sites (STSs) (Hudson et al. 1995) was consulted on the Whitehead Institute (WI) Internet site (www-genome.wi.mit.edu/~~One Kendall Square, Building 300, Cambridge, MA 02139-1561~~). CEPH mega-YACs were obtained from the YAC Screening Centre Leiden (YSCL, the Netherlands) and from CEPH (Paris, France). The YACs were analyzed for the presence of STSs and STRs, previously located between D18S51 and D18S61, by touchdown PCR amplification. Information on the STSs/STRs was obtained from the WI, GDB, Généthon, CHLC and GenBank sites on the Internet. Thirty PCR cycles consisted of: denaturation at 94°C for 1 min, annealing (2 cycles for each temperature) starting from 65°C and decreasing to 51°C for 1.5 min and extension at 72°C for 2 min. This was followed by 10 cycles of denaturation at 94°C for 1 min, annealing at 50°C for 1.5 min and extension at 72°C for 2 min. A final extension step was performed for 10 min at 72°C. Amplified products were visualized by electrophoresis on a 1% TBE agarose gel and ethidium bromide staining.

Please replace the paragraph on page 29, lines 1-26, with the amended paragraph as follows:

D18S68, common to all 3 maps, was taken as the map anchor point, and the genetic distance in cM or cR of the other markers relative to D18S68 are given. The marker order is in good agreement with the order of the markers on the recently published chromosome 18 radiation hybrid map (Giacalone et al. (1996) Genomics 37:9-18) and the WI YAC-contig map (www-genome.wi.mit.edu/~~ One Kendall Square, Building 300, Cambridge, MA 02139-1561~~). However, a few discrepancies with other maps were observed. The only discrepancy with the Généthon map is the reversed order of D18S465 and D18S477. Two discrepancies were observed with the Marshfield map (www.marshmed.org/genetics/ ~~Center for Medical Genetics, 1000 North Oak Avenue, Marshfield, WI, 54449-5790~~). The present inventors mapped D18S346 above D18S55 based on maternal haplotypes, but on the Marshfield maps D18S346 is located between D18S483 and D18S979. The inventors also places D18S817 below D18S979, but on the Marshfield map this marker is located between D18S465 and D18S477. However, the

location of D18S346 and D18S817 is in agreement with the chromosome 18 radiation hybrid map of Giacalone et al. (1996). One discrepancy was also observed with the WI radiation hybrid map (www-genome.wi.mit.edu/ ~~One Kendall Square, Building 300, Cambridge, MA 02139-1561~~), in which D18S68 was located below D18S465. However, the inventors as well as other maps places this marker above D18S55.

Please replace the paragraph on page 32, lines 7-30, with the amended paragraph as follows:

Before the fine mapping the candidate region was flanked by D18S51 and D18S61, which are separated by a genetic distance if 15.2 cM on the Marshfield map or 13.1 cM on the Généthon map. The informative recombinants with D18S51 and D18S61 were observed in 2 affected individuals (II.10 and II.11 in Fig. 13). However, since no other markers were tested within the candidate region it was not known whether these individuals actually shared a region identical-by-descent (IBD). The additional genetic mapping data now indicate that all affected individuals are sharing alleles at D18S969, D18S1113, D18S876 and D18S477 (Fig. 13, boxed haplotype). Also, alleles from markers D18S483 and D18S465 are probably IBD, but these markers were not informative in the affected parent I.1. Obligate recombinants were observed with the STR markers D18S68, D18S346, D18S979 and D18S817 (Table 2, fig. 13) Since discrepancies between different maps were observed for the locations of D18S346 and D18S817, the present inventors used D18S68 and D18S979 to redefine the candidate region for BP disease. The genetic distance between these 2 markers is 8.9 cM based on the Marshfield genetic map (www.marshmed.org/genetics/~~Center for Medical Genetics, 1000 North Oak Avenue, Marshfield, WI, 54449-5790~~).

Please replace the paragraph on page 32, line 34 through page 33, line 18, with the amended paragraph as follows:

According to the WI integrated map 56 CEPH megaYACs are located in the initial candidate region contained between D18S51 and D18S61 (Chumakov et al. (1995) Nature 377 Suppl., De bruyn et al. (1996)). From these YACs, those were selected that were located in the

region between D18S60 and D18S61. D18S51 is not presented on the WI map, but is located close to D18S60 according to the Marshfield genetic map (www.marshmed.org/genetics/ ~~Center for Medical Genetics, 1000 North Oak Avenue, Marshfield, WI, 54449-5790~~). To limit the number of potential chimaeric YACs, YACs were eliminated that were also positive for non-chromosome 18 STSs. As such, 25 YACs were selected (see Figure 14), and placed in a contig based on the technique of YAC contig mapping, i.e. sequences from sequence tagged sites (STSs), simple tandem repeats (STRs) and expressed sequenced tags (ESTs), known to map between D18S60 and D18S61, were amplified by PCR on the DNA from the YAC clones. The STS, STR and EST sequences used, are described from page 36 to 54. Positive YAC clones were assembled in a YAC contig map (Figure 14).